Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (previously presented) A method of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors, said isolated ligand comprising a heregulin polypeptide selected from the group consisting of heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, heregulin-β3 (SEQ ID NO: 7) fragments, and variants thereof wherein

said variants have at least 95% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments are effective to activate HER2 and/or HER 3 receptors, and wherein

said heregulin-α (SEQ ID NO: 1) fragments comprise the amino acid sequence between HRG-α amino acid residues 175 to 230, and the amino terminus of a HRG-α fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 226 of SEQ ID NO: 1, and the carboxy terminus of a HRG-α fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 265 and amino acid residue 286 of SEQ ID NO: 1,

said heregulin-β1 (SEQ ID NO: 3) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 3, and the amino terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine

residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 3, and the carboxy terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 3;

said heregulin-β2 (SEQ ID NO: 5) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 5, and the amino terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 5, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 5;

said heregulin-β3 (SEQ ID NO: 7) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 7, and the amino terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 7, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 285 of SEQ ID NO: 7; and

said variants of said fragments are selected from the group of variants consisting of substitutions, insertions, or deletions of at heregulin-α (SEQ ID NO: 1) amino acid residues 2, 3, 8, 9, 23, 24, 33, 34, 42, 43, 45, 46, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226, 234, 240, 254, 256, 265, 272, 273, 278, 279, 285-309, 437, 609-611, or at corresponding residues of heregulin-β1 (SEQ ID NO: 3), heregulin-β (SEQ ID NO: 3), or heregulin-β3 (SEQ ID NO: 7).

2. (canceled)

3. (currently amended) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a human heregulin polypeptide ~~or a~~ fragment selected from the group consisting of human heregulin-α (SEQ ID NO: 1) fragments, human heregulin-β1 (SEQ ID NO: 3) fragments, and human heregulin-β2 (SEQ ID NO: 5) fragments~~,~~.

4. (canceled)

5. (canceled)

6. (previously presented) A method of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a recombinant human heregulin polypeptide selected from the group consisting of human heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, heregulin-β3 (SEQ ID NO: 7) fragments, and variants thereof wherein

said variants have at least 95% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments are effective to activate HER2 and/or HER 3 receptors, and wherein

said heregulin-α (SEQ ID NO: 1) fragments comprise the amino acid sequence between HRG-α amino acid residues 175 to 230 of SEQ ID NO: 1, and the amino terminus of a HRG-α fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 226 of SEQ ID NO: 1, and the carboxy terminus of a HRG-α

fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 265 and amino acid residue 286 of SEQ ID NO: 1;

said heregulin-β1 (SEQ ID NO: 3) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 3, and the amino terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 3, and the carboxy terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 3;

said heregulin-β2 (SEQ ID NO: 5) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 5, and the amino terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 5, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 5;

said heregulin-β3 (SEQ ID NO: 7) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 7, and the amino terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 7, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 285 of SEQ ID NO: 7; and

said variants of said fragments are selected from the group of variants consisting of substitutions, insertions, or deletions of at heregulin-α (SEQ ID NO: 1) amino acid residues 2, 3, 8, 9, 23, 24, 33, 34, 42, 43, 45, 46, 62-67, 86, 87, 110, 111, 123, 124,

134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226, 234, 240, 254, 256, 265, 272, 273, 278, 279, 285-309, 437, 609-611, or at corresponding residues of heregulin-β1 (SEQ ID NO: 3), heregulin-β (SEQ ID NO: 3), or heregulin-β3 (SEQ ID NO: 7) .

7. (previously presented) The method of claim 1, wherein the supporting cell is in a cochlear implant.

8. (previously presented) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is administered at a daily dose of about 1 µg/kg to 100 mg/kg.

9. (canceled)

10. (original) The method of claim 1, wherein the contacting is by administration to a patient in need thereof.

11. (previously presented) The method of claim 6, wherein the heregulin fragment is rHRG-β1-177-244.

12. (original) The method of claim 1, wherein the inner-ear-supporting cell is in the utricle or cochlea.

13. (canceled)

14. (previously presented) A method of increasing the number of inner-ear-supporting cells, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, heregulin-β3 (SEQ ID NO: 7) fragments, and variants thereof, wherein

said variants have at least 95% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments are effective to activate HER2 and/or HER 3 receptors, and wherein

said heregulin-α (SEQ ID NO: 1) fragments comprise the amino acid sequence between HRG-α amino acid residues 175 to 230, and the amino terminus of a HRG-α fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 226 of SEQ ID NO: 1, and the carboxy terminus of a HRG-α fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 265 and amino acid residue 286 of SEQ ID NO: 1;

said heregulin-β1 (SEQ ID NO: 3) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 3, and the amino terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 3, and the carboxy terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 3;

said heregulin-β2 (SEQ ID NO: 5) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 5, and the amino terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 5, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 5;

said heregulin-β3 (SEQ ID NO: 7) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 7, and the amino terminus of a HRG-β2 fragment results from the

cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 7, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 285 of SEQ ID NO: 7; and

said variants of said fragments are selected from the group of variants consisting of substitutions, insertions, or deletions of at heregulin-α (SEQ ID NO: 1) amino acid residues 2, 3, 8, 9, 23, 24, 33, 34, 42, 43, 45, 46, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226, 234, 240, 254, 256, 265, 272, 273, 278, 279, 285-309, 437, 609-611, or at corresponding residues of heregulin-β1 (SEQ ID NO: 3), heregulin-β (SEQ ID NO: 3), or heregulin-β3 (SEQ ID NO: 7).

15. (canceled)

16. (currently amended) A method of treating a hair cell related hearing disorder, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, , heregulin-β3 (SEQ ID NO: 7) fragments, wherein

said variants have at least 95% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments are effective to activate HER2 and/or HER 3 receptors, and wherein

said heregulin-α (SEQ ID NO: 1) fragments comprise the amino acid sequence between HRG-α amino acid residues 175 to 230, and the amino terminus of a HRG-α fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine,

valine, or methionine residue between amino acid residue 1 and amino acid residue 226 of SEQ ID NO: 1, and the carboxy terminus of a HRG-α fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 265 and amino acid residue 286 of SEQ ID NO: 1;

said heregulin-β1 (SEQ ID NO: 3) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 3, and the amino terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 3, and the carboxy terminus of a HRG-β1 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 3;

said heregulin-β2 (SEQ ID NO: 5) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 5, and the amino terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 5, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 302 of SEQ ID NO: 5;

said heregulin-β3 (SEQ ID NO: 7) fragments comprise amino acid residues 175 to 230 of SEQ ID NO: 7, and the amino terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine residue between amino acid residue 1 and amino acid residue 212 of SEQ ID NO: 7, and the carboxy terminus of a HRG-β2 fragment results from the cleavage of a peptide bond adjacent to an arginine, lysine, valine, or methionine between amino acid residue 251 and amino acid residue 285 of SEQ ID NO: 7; and

said variants of said fragments are selected from the group of variants consisting of substitutions, insertions, or deletions of at heregulin-α (SEQ ID NO: 1) amino acid

residues 2, 3, 8, 9, 23, 24, 33, 34, 42, 43, 45, 46, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226, 234, 240, 254, 256, 265, 272, 273, 278, 279, 285-309, 437, 609-611, or at corresponding residues of heregulin-β1 (SEQ ID NO: 3), heregulin-β (SEQ ID NO: 3), or heregulin-β3 (SEQ ID NO: 7).

17. (canceled)

18. (canceled)

19. (previously presented) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a heregulin-β fragment variant capable of binding to the HER2 or HER3 receptor, wherein said heregulin-β fragment variant is selected from the group consisting of heregulin-β fragment variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions of the mature polypeptide within SEQ ID NO:3 are at positions S207, H208, L209, V210, K211, E214, E216, K217, T218, V221, N222, G223, G224, E225, M228, V229, K230, D231, N234, P235, S236, R237, Y238, L239, K241, P243, N244, E245, T247, G248, D249, Q252, N253, Y254, M256, S258, and F259 of SEQ ID NO: 3.

20. (previously presented) The method of claim 14, wherein the activating ligand is a heregulin-β fragment variant, capable of binding to the HER2 or HER3 receptor, wherein said heregulin-β variant is selected from the group consisting of heregulin-β variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206,

R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions of the mature polypeptide within SEQ ID NO:3 are at positions S207, H208, L209, V210, K211, E214, E216, K217, T218, V221, N222, G223, G224, E225, M228, V229, K230, D231, N234, P235, S236, R237, Y238, L239, K241, P243, N244, E245, T247, G248, D249, Q252, N253, Y254, M256, S258, and F259 of SEQ ID NO: 3.

21. (previously presented) The method of claim 16, wherein the activating ligand is a heregulin-β fragment variant, capable of binding to the HER2 or HER3 receptor, wherein said heregulin-β variant is selected from the group consisting of heregulin-β variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions of the mature polypeptide within SEQ ID NO:3 are at positions S207, H208, L209, V210, K211, E214, E216, K217, T218, V221, N222, G223, G224, E225, M228, V229, K230, D231, N234, P235, S236, R237, Y238, L239, K241, P243, N244, E245, T247, G248, D249, Q252, N253, Y254, M256, S258, and F259 of SEQ ID NO: 3.

22. (previously presented) The method of claim 1, wherein the inner-ear-supporting cell is in the cochlea.

23. (previously presented) The method of claim 6, wherein the inner-ear-supporting cell is in the cochlea.

24. (previously presented) The method of claim 11, wherein the inner-ear-supporting cell is in the cochlea.

25. (new) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a heregulin-β fragment variant capable of binding to the HER2 or HER3 receptor, wherein said heregulin-β fragment variant is selected from the group consisting of heregulin-β fragment variants having an amino acid substitution at one or more amino acid residues corresponding to positions P213, N214, and E215 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions of the mature polypeptide within SEQ ID NO:3 are at positions P243, N244, and E245 of SEQ ID NO: 3.

26. (new) The method of claim 14, wherein the activating ligand is a heregulin-β fragment variant, capable of binding to the HER2 or HER3 receptor, wherein said heregulin-β variant is selected from the group consisting of heregulin-β variants having an amino acid substitution at one or more amino acid residues corresponding to positions P213, N214, and E215 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions of the mature polypeptide within SEQ ID NO:3 are at positions P243, N244, and E245 of SEQ ID NO: 3.

27. (new) The method of claim 16, wherein the activating ligand is a heregulin-β fragment variant, capable of binding to the HER2 or HER3 receptor, wherein said heregulin-β variant is selected from the group consisting of heregulin-β variants having an amino acid substitution at one or more amino acid residues corresponding to positions P213, N214, and E215 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions of the mature polypeptide within SEQ ID NO:3 are at positions P243, N244, and E245 of SEQ ID NO: 3.